REMARKS

I. Petition for Extension of Time

A final Office Action was mailed March 1, 2005, and a Notice of Appeal was filed August 31, 2005. Applicants herewith petition the Commissioner for Patents for a one-month extension of time. Authorization is given to charge the extension of time fee of $60.00 (37 C.F.R. §§1.136 and 1.17) to Deposit Account No. 23-1703. Any deficiency or overpayment should be charged or credited to the above numbered deposit account.

II. Restriction Requirement of Record

The restriction requirement of record includes the following elected embodiments:

- medical device – stent
- matrix – fullerene
- antibody attachment – covalent
- vessel type – artery
- matrix attachment – covalent.

In the event that the amended independent claims are found to define an allowable genus, the Examiner is respectfully requested to withdraw the restriction requirement and to rejoin the withdrawn claims and/or embodiments for examination in the present application.

III. Amendments to the Specification and Claims

The Abstract has been amended by the deletion of the article "a" from the third sentence as suggested by the Examiner.

The claims have been amended to clarify that the recited coating renders the claimed medical device compatible for *in vivo* attachment and proliferation of cells on the surface thereof. The claims have also been amended to clarify that *in vivo* attachment and proliferation of cells is possible when the medical device is coated with a coating composition comprising a type of antibody which reacts with an endothelial cell surface antigen, and one or more layers of a matrix. Amended claim 2 and new claims 77-79 provide that the claimed invention is characterized by antibodies, or fragments thereof, of the type which reacts with an endothelial cell surface antigen.

Applicants submit that no new matter has been introduced by the amendments.

IV. Claim Rejections – 35 U.S.C. §112

Claims 1, 18, 20, 25, 29, 38, 63, 70 and 74 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. In response thereto, the expression "combinations of the antibodies and fragments" has been deleted from claims 1, 18, 25, 29 and 38, whereas the expression "mixtures thereof" has been deleted from claims 20, 63, 70 and 74.

Claims 64, 65, 67, 68, 71, 72, 75 and 76 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. These claims have been amended as suggested by the Examiner, i.e., first limiting the matrix to a fullerene, and then further limiting the fullerene.

Withdrawal of the §112, first and second paragraphs, is requested.

V. Claim Rejections – 35 U.S.C. §103

All of the obviousness rejections of record have one thing in common. They are based on the combination of the following two references: Dekker, A. et al, *Thrombosis and Haemostasis*, "Improved Adhesion and Proliferation of Human Endothelial Cells on Polyethylene Precoated with Monoclonal Antibodies Directed against Cell Membrane Antigens and Extracellular Matrix Proteins", F.K. Schattauer Verlagsgesellschaft mbH (Stuttgart) 66(6) 715-724 (1991) ("Dekker"), and US 5,310,669 to Richmond et al. ("Richmond"). In certain instances, a tertiary reference is cited.

With this commonality in mind, the obviousness rejections as set forth in the final Office Action can be divided into the following two groups:

Group 1: Dekker in view of Richmond
(¶¶9-12 and 15 of the Office Action)

- medical device claims 1, 2, 4, 5, 7-9, 38, 39, 63 and 64, and
- method of treatment claims 29-32, 74 and 75, and

Group 2: Richmond in view of Dekker
(¶¶13 and 14 of the Office Action)

- composition claims 18, 20-24 and 67, and
- method of coating claims 25, 27, 70 and 71.

Each of Dekker and Richmond has been discussed at length by Applicants in their previous responses to the same §103 rejections of record. Accordingly, Applicants rely on and direct the Examiner's attention to the Remarks with respect to Dekker and Richmond in the Amendments, filed January 16, 2004 and September 27, 2004, respectively. However, to be fully responsive to the final Office Action, Applicants provide the following summary.

Dekker is directed to an *in vitro* study of endothelial cell seeding and proliferation on the surface of an antibody-coated polyethylene substrate. Dekker discloses that attachment of seeded endothelial cells is achieved with a surface coating of monoclonal antibodies CLB-HEC 19 and CLB-HEC-3477 directed against endothelial cell-specific membrane antigens (pp. 717-718 and Figure 3). It is further disclosed that proliferation did not occur on these surface-adsorbed antibodies (pp. 718-719 and Figures 5-6). Rather, at the end of the Summary and at page 722, column 2, Dekker reports that attachment and proliferation require two categories of monoclonal antibodies: (1) antibodies directed against plasma membrane antigens of human endothelial cells and (2) antibodies directed against the adhesive proteins von Willebrand factor and fibronectin.

Unexpectedly, and in contrast to Dekker, the claimed medical device and coating composition provide a surface that achieves *in vivo* selection and adhesion of circulating cells with a coating of only one class of antibodies. Advantageously, after attachment to the coated surface, the endothelial cells proliferate to form a surface that decreases and/or prevents restenosis and thrombosis.

Richmond is similar to Dekker in that the disclosure of Richmond is limited to the attachment and growth of seeded cells in an *in vitro* environment, e.g., a cell culture substrate. Furthermore, Richmond does not disclose or suggest a matrix with specific antibodies attached thereto for binding endothelial cells.

A. Declaration under 37 C.F.R. §1.132 of Michael John Bradley Kutryk (the "Declaration")

Applicants rely on their arguments of record that the combination of Dekker and Richmond, whether taken alone or in combination with a tertiary reference, does not suggest the claimed invention. In support, Applicants submit a Declaration under 37 C.F.R. §1.132 in the

name of one of the inventors of the claimed invention. In the following discussion, the symbol (¶) refers to the paragraph of the Declaration where support for the statement can be found.

The thrust of the Declaration is the expert opinion that a person of ordinary skill in the art, at the time the claimed invention was made, would not have been motivated to combine Dekker and Richmond with a reasonable expectation of successfully arriving at the claimed invention (¶6). It is an undisputable fact that Dekker and Richmond are limited to *in vitro* studies under static conditions (¶¶7-8). At page 12 of the final Office Action, the Examiner states that the combination of prior art, including Dekker and Richmond, would produce a structure that "allows for *in vivo* attachment of cells, which they do". For the reasons set forth in the Declaration, it is respectfully submitted that the Examiner's statement suggests an improper reliance on hindsight.

Specifically, a showing of obviousness requires a motivation or suggestion to combine or modify prior art references ***coupled with a reasonable expectation of success*** (M.P.E.P. §2143.02). Therefore, the correct standard for establishing a *prima facie* case of obviousness is not, as proposed by the Examiner, whether the combination of prior art references produces a structure that "allows for *in vivo* attachment", but rather whether the combination has a reasonable expectation of success. Furthermore, whether the combination of prior art references has reasonable expectation of success is determined ***at the time the invention was made*** (M.P.E.P. §2143.02). Again, it is respectfully submitted that the Examiner's statement that the cited combination of prior art "allows for *in vivo* attachment of cells, which they do" suggests an improper reliance on hindsight.

At the time the claimed invention was made, a person of ordinary skill in the art would have reasonably expected that shear forces, i.e., *in vivo* under conditions of flow, would quickly wash off any surface-adsorbed antibodies as disclosed by Dekker and Richmond (¶9). Without a surface-coating of adsorbed antibodies, the capture *in vivo* of circulating endothelial cells and proliferation of captured cells to bring about an inhibition of restenosis would not and could not have reasonably been expected in view of the prior art (¶9). Accordingly, a person of ordinary skill in the art would not have been motivated to combine Dekker and Richmond with a reasonable expectation of successfully producing the claimed medical device for implantation into a patient, wherein the medical device has a coating comprising a matrix layer and antibodies

with specificity to bind cell surface antigens of endothelial cells, or progenitors thereof, *in vivo* (¶9).

Therefore, at the time the claimed invention was made, it was indeed unexpected that a single type of antibody which binds a specific cell membrane antigen could be utilized to capture cells *in vitro* or *in vivo*, and support proliferation of the immobilized cells (¶10).

Advantageously, the claimed invention inhibits restenosis (¶12). The Declaration provides a comparison, *in vivo* and *in vitro*, of uncoated and coated stents. The data shows convincingly a superior therapeutic result. Stents which are coated in accordance with the claimed invention, i.e., with a matrix layer and an antibody which reacts with an endothelial cell surface antigen, were covered more rapidly with more endothelial cells which, when implanted in coronoary arteries, provided a remarkably thinner blood vessel wall and larger luminal diameter (¶¶12-14). This result could not reasonably have been expected at the time the claimed invention was made in view of the reasonable expectation that shear forces, i.e., *in vivo* under conditions of flow, would quickly wash off any surface-adsorbed antibodies as disclosed by Dekker and Richmond (¶9).

Moreover, it is the expert opinion of the declarant that it is not possible to predict with reasonable certainty the properties that a medical device will exhibit *in vivo* when compared to *in vitro* since the conditions vary tremendously. The fact that the claimed invention yielded the reported results was unexpected and could not have been reasonably predicted (¶19).

B. <u>Claim Rejections – Dekker in view of Richmond</u>

In this Section V(B), Applicants will address the obviousness rejection under 35 U.S.C. §103(a) of medical device claims 1, 2, 4, 5, 7-9, 38, 39, 63 and 64 and method of treatment claims 29-32, 74 and 75 (¶¶9-12 and 15 of the Office Action). The §103 rejection of each of these claims is based on the same combination of Dekker as the primary reference and Richmond as the secondary reference. In certain instances, a tertiary reference is cited.

Dekker reports that cell proliferation was completely absent and even detachment of the endothelial cells occurred when a polyethylene substrate was coated with one-type of antibody, i.e., antibodies against an endothelial cell surface antigen. To obtain endothelial cell proliferation *in vitro*, Dekker further reports that a second-type of antibody is required, i.e.,

antibodies directed against extracellular matrix protein (page 722, column 1, lines 52-56, and column 2, last paragraph; Figs. 5 and 6).

Contrary to Dekker , the Declaration provides data showing that a single type of antibody which binds a specific cell membrane antigen can be utilized to capture cells *in vitro or in vivo*, and support proliferation of the immobilized cells in both instances (¶¶12-14). A recitation of the intended use of the claimed invention, i.e., *in vivo* capture and proliferation, is reflected in a claimed structural difference in comparison to Dekker. Specifically, the claimed invention has been amended to clarify that the medical device consists of a coating which renders the medical device compatible for *in vivo* attachment and proliferation of cells on the surface thereof. The coating composition consists of a matrix and one class of antibodies which react with an endothelial cell surface antigen. Dekker admittedly is not capable of performing the intended use as defined by the amended claims.

Furthermore, on page 722, column 2, Dekker concludes that the use of whole antibody would not be feasible, since the "[p]latelet activation by adsorbed intact antibody is probably mediated by the Fc parts of the IgG molecules." (¶15) This conclusion is contrary to the result that is obtained with the claimed invention. All of the *in vivo* experiments presented in the Declaration were performed using intact antibodies on the coating. As such Dekker can be said to teach away from the claimed invention.

Medical device claims 1, 2, 4, 7, 9, 38, 39, 63 and 64 are rejected under 35 U.S.C. §103(a) as being unpatentable over Dekker in view of Richmond. The secondary reference to Richmond is cited by the Examiner for the alleged disclosure of a substrate surface coated with a fullerene matrix for attaching and growing cells.

The entirety of the Richmond disclosure is limited to cell culture substrates for *in vitro* biological applications, e.g., growing cells in Petri dishes. Richmond is silent with respect to any actual medical application, and there is nothing in Richmond to suggest that cells growing on the static culture substrates disclosed by Richmond could withstand shear forces *in vivo* under conditions of flow. Therefore, a person of ordinary skill in the art would reasonably expect that any surface-adsorbed antibodies disclosed by Richmond would be quickly washed off by such *in vivo* shear forces (¶¶9, 16). Accordingly, at the time the claimed invention was made, Richmond did not and could not offer a reasonable expectation of successfully using a fullerene-coated substrate to promote the attachment of endothelial cells *in vivo* in the first place, which

attachment would result in proliferation of the cells, and formation of functional endothelium *in vivo*.

Furthermore, Richmond does not disclose a fullerene matrix with specific antibodies attached thereto for binding endothelial cells. The data presented in ¶¶12-14 show that medical devices having different synthetic or naturally occurring matrices in the coating, e.g., Dextran, fullerene and gelatin, in combination with the antibody of the claimed invention resulted in specific binding to an endothelial cell surface antigen, proliferation of the bound cells and inhibition of restenosis. These results were unexpected and not predictable from Richmond, whether taken alone or in combination with Dekker (¶17).

Finally, the data described in ¶13 of the Declaration show that a single antibody specific to an endothelial cell surface antigen in combination with a fullerene matrix in the coating of the medical device promotes increased binding and proliferation of endothelial cells. This result is contrary to the data in Dekker et al. and Richmond et al. which, respectively, assert that two antibody types are needed for *in vitro* cell growth (Dekker at Abstract) and that growth factors are required in the incubation medium to promote *in vitro* cell growth (Richmond et al. col. 3 lines 48-64) (¶18).

For all of the foregoing reasons, the combination of Dekker and Richmond does not suggest the invention of medical device claims 1, 2, 4, 7, 9, 38, 39, 63 and 64. Moreover, the Declaration provides the expert opinion that a person of ordinary skill in the art, at the time the claimed invention was made, would not have been motivated to combine Dekker and Richmond with a reasonable expectation of successfully arriving at the claimed invention (¶6). Withdrawal of the §103 rejection of claims 1, 2, 4, 7, 9, 38, 39, 63 and 64 is requested.

Medical device claim 5 is rejected under 35 U.S.C. §103(a) as being unpatentable over the combination of Dekker, Richmond and US 5,688,486 to Watson et al. ("Watson"). Medical device claim 8 is rejected under 35 U.S.C. §103(a) as being unpatentable over the combination of Dekker, Richmond and in view Asahara et al., Science 275: 964-967 (1997) ("Asahara"). Method of treatment claims 29-32, 74 and 75 are rejected under 35 U.S.C. §103(a) as being unpatentable over the combination of Dekker, Richmond and Bos et al., Archives Phsio. Biochem 106; 100115 (1998) ("Bos").

Applicants respectfully submit that a *prima facie* case of obviousness has not been established. Dekker does not disclose or suggest the claimed invention, and none of the

secondary or tertiary references overcome the failure of Dekker to suggest the claimed invention. Withdrawal of the §103 rejection of medical device claims 5 and 8 and method of treatment claims 29-32, 74 and 75 is requested.

C. Claim Rejections – Richmond in view of Dekker

In this Section V(C), Applicants will address the obviousness rejection under 35 U.S.C. §103(a) of composition claims 18, 20-24 and 67 and method of coating claims 25, 27, 70 and 71 (¶¶13 and 14 of the Office Action). These claims are directed to a composition and method for coating a medical device with the composition comprising a matrix and a therapeutically effective amount of at least one type of antibody that reacts with an endothelial cell surface antigen. With respect to the §103 rejection of the composition claims, the Examiner again relies on Dekker and Richmond. However, in this case, the primary reference is Richmond and the secondary reference is Dekker.

Independent claims 18 and 25 recite that the claimed coating composition comprises a matrix and a type of antibody which renders the medical device compatible for *in vivo* attachment and proliferation of cells on the surface of the coated medical device. As discussed in Section V(B), above, the respective disclosure of Richmond and Dekker is limited to the *in vitro* seeding of coated or uncoated surfaces with endothelial cells. Furthermore, as noted by the Examiner, Richmond is silent with respect "to the antibody reacting with an endothelial cell antigen and the substrate being a medical device" (Office Action at page 6 and 7). Thus, the Examiner relies on Dekker as the secondary reference.

Dekker admits the inability to achieve cell proliferation with the composition and method of claims 18 and 25, respectively. Similarly, the tertiary reference to Asahara does not disclose or suggest *in vivo* proliferation. A stated in the abstract, Asahara discloses the isolation of putative endothelial progenitor cells from human peripheral blood and *in vitro* differentiation of these cells.

The correct standard for establishing a *prima facie* case of obviousness is not, as proposed by the Examiner, whether the combination of prior art references "allows for *in vivo* attachment", but rather whether the combination has a reasonable expectation of success (M.P.E.P. §2143.02). Whether the combination of prior art references has reasonable expectation of success is determined at the time the invention was made (M.P.E.P. §2143.02). The

Declaration provides the expert opinion that a person of ordinary skill in the art, at the time the claimed invention was made, would not have been motivated to combine Dekker and Richmond with a reasonable expectation of successfully arriving at the claimed invention (¶6).

For all of the foregoing reasons, Applicants submit that none of the cited references, whether taken alone or in combination, suggests a coating composition or method that renders a medical device compatible for *in vivo* attachment and proliferation of cells on the surface of the coated device. As such, a *prima facie* case of obviousness based on the combination of Richmond and Dekker has not been established with respect to claims 18, 20-22, 24, 25 and 27. The tertiary reference to Asahara does not overcome the failure of Richmond and Dekker to suggest the claimed invention and, therefore, a *prima facie* case of obviousness with respect to claim 23 has not been established. Withdrawal of the §103 rejection of composition claims 18, 20-25, 27, 67, 70 and 71 is requested.

In the event that the obviousness rejection of the claimed composition is maintained, Applicants submit that the claimed coating method, i.e., claim 25, is nevertheless patentable since, in such case, the claimed coating method must be deemed to represent a new use of an old composition.

VI. Double Patenting

Claims 1, 2, 4, 5, 7-9, 29-32, 38, 39, 63, 64, 74 and 75 are provisionally rejected under the judicially created doctrine of obviousness type double patenting as allegedly being unpatentable over claims 1-3, 7-15, 25-33, 35-39, 42-47, 49 and 50 of co-pending U.S. Patent Application Serial No. 10/360,567. The Examiner alleges that the conflicting claims, although not identical, are not patentably distinct from each other. It is further alleged that the claims of the current application include all of the limitations of the co-pending application and are broader.

Since the rejection is provisional, Applicants will respond to the rejection at such time that the claims of either application have been patented.

VII. Allowable Subject Matter

Applicants are appreciative of the allowance of claims 41 and 45. Claims 65, 68, 72 and 76 would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

For all of the preceding reasons, Applicants submit that the claimed invention as defined by all of the pending claims is patentable. Therefore, at this time, it is respectfully submitted that there is no reason to limit a patent for the claimed invention to the embodiments of the presently allowable claims.

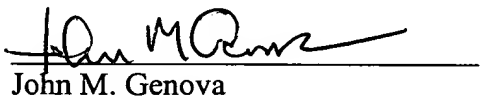
CONCLUSION

Applicants have made a good faith attempt to respond to the Office Action. The pending claims are directed to patentable subject matter. Accordingly, Applicants request reconsideration and allowance of the claims.

Any additional fee due in connection with this communication should be charged to Deposit Account No. 23-1703.

Dated: November 3, 2005

Respectfully submitted,



John M. Genova
Reg. No. 32,224

Customer No. 07470
Attorney Direct Dial: (212) 819-8832